CARDIOVASCULAR RESPONSE OF MONKEYS TO SUPRALETHAL DOSES OF MIXED GAMMA-NEUTRON RADIATION

ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
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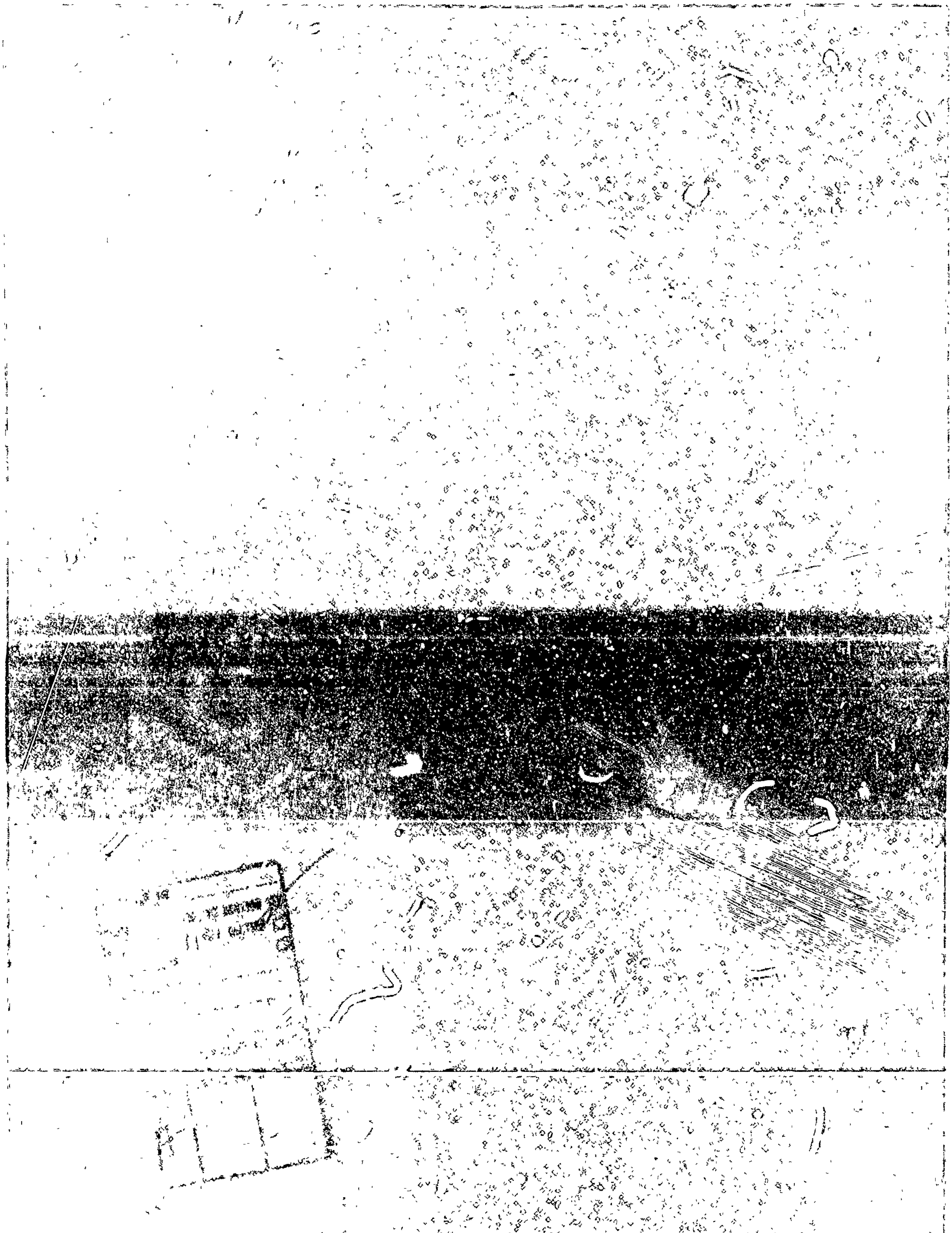

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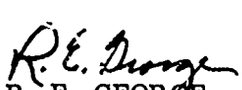

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FOREWORD
(Nontechnical summary)

In the monkey a transient decrement in ability to react to a stimulus or to perform a learned task frequently occurs within a few minutes after supralethal doses of 2000 to 6600 rads of radiation. A decrease in arterial pressure has also been observed in animals receiving doses of radiation in this range during the period of incapacitation.

In the present study monkeys were given 2000, 4000, 15,000, or 50,000 rads of mixed gamma-neutron radiation to determine if changes in the cardiovascular system occur before or during early transient incapacitation (ETI) which may contribute to the decrement observed at this range of supralethal doses. One week before irradiation catheters were surgically placed in the femoral artery and vein and advanced into the aorta and vena cava. The catheters were flushed daily with physiological saline containing 0.1 percent heparin. The mean arterial pressure and heart rate were monitored at 24 hours before irradiation and continuously from approximately 20 minutes preirradiation until 1 hour postirradiation. Red blood cells labeled with ^{51}Cr and ^{125}I labeled albumin were intravenously injected at 20 minutes before irradiation and blood was withdrawn at 5 minutes before and at 2, 7, 15, 30, and 60 minutes postirradiation for blood volume and plasma chemistry determinations.

A significant decrease in the mean arterial pressure occurred within 1 to 2 minutes postirradiation in the 2000-, 4000-, and 15,000-rad groups and continued for 10 to 20 minutes. The pressure then returned toward but never reached

preirradiation levels. A small decline in pressure was observed in the 50,000-rad group but the decrease was not significant until 25 to 30 minutes postirradiation.

The heart rate increased significantly in the 4000-, 15,000-, and 50,000-rad groups. The rate of increase after irradiation appeared to be a function of dose. However, the heart rates of the 15,000-rad group varied considerably after the initial increase until approximately 8 minutes postirradiation. After this period of fluctuation the heart rates of this dose group stabilized at a mean level which was greater than the preirradiation value.

Except for the 50,000-rad group and the early fluctuation in the 15,000-rad group, the heart rates increased as the mean arterial pressure decreased. It appears that the decrease in pressure in the lower dose groups is the result of vascular engorgement and that the controlling mechanism of this phenomenon is inhibited or destroyed at a dose of 50,000 rads.

No significant changes were noted in the plasma volume, red cell volume or the plasma concentration of sodium, potassium, chloride, total protein, creatinine, glutamic oxalacetic transaminase, lactic dehydrogenase, or aldolase at the periods sampled after irradiation. It would appear that the early transient incapacitation observed in the monkey after supralethal doses of radiation is not a result of changes in either the blood volume or the chemical constituents of plasma measured.

ABSTRACT

Monkeys were given a pulsed dose of 2000, 4000, 15,000, or 50,000 rads of mixed gamma-neutron radiation to determine if changes in the cardiovascular system occur before or during early transient incapacitation (ETI) which may contribute to the decrement observed after supralethal doses of radiation. The mean arterial pressure, heart rate, blood volume, and some plasma chemistry values were determined in catheterized monkeys maintained in restraining chairs before and for 1 hour following irradiation or until death. The mean arterial pressure decreased significantly within 1 to 2 minutes following irradiation in the 2000-, 4000-, and 15,000-rad groups and remained depressed until 10 to 20 minutes postexposure before returning toward normal values. No significant decrease in the mean arterial pressure was observed in the 50,000-rad group until 25 to 30 minutes postirradiation. The heart rate increased significantly in the 4000-, 15,000-, and 50,000-rad groups following irradiation. No significant changes were observed in the blood volume or plasma components measured. It appears that the mechanisms which result in an early temporary postirradiation hypotension in the monkeys at the lower supralethal doses of radiation are either inhibited or destroyed with a 50,000-rad dose.

I. INTRODUCTION

A description of the gross decrement suffered by monkeys (Macaca mulatta) after supralethal doses of radiation has been reported by Seigneur and Brennan.[10] In other studies, when the monkey received doses up to 6600 rads, a decrease in the mean arterial pressure and a behavioral decrement have been observed during the period designated by Seigneur and Brennan as early transient incapacitation (ETI). In most instances both indices return toward preirradiation values within 10 to 20 minutes postirradiation.[2-4,8]

This study was initiated to determine if changes in plasma or red cell volume and/or ionic changes in the plasma contribute to the decrease in arterial pressure observed in the monkey after low to moderately high supralethal doses of radiation and to initially determine the effects of a very high supralethal dose of radiation on the cardiovascular system. Monkeys were given a pulsed mixed gamma-neutron dose of 2000, 4000, or 15,000 rads, where survival time is dependent upon dose, or 50,000 rads, where ETI was not observed in an earlier study.[10] The arterial pressure, heart rate, blood volume, and some plasma chemistry values were measured before irradiation and up to 1 hour postirradiation.

II. MATERIALS AND METHODS

Young adult monkeys (Macaca mulatta) of both sexes, ranging in age from 2 to 4 years and weighing 2.7 to 5.0 kg, were utilized in this study.

Catheters were surgically placed in the femoral artery and vein of the anesthetized monkey and advanced into the aorta and vena cava. After surgery the animals were maintained in restraining chairs for approximately 1 week before irradiation.

The catheters were flushed daily with physiological saline containing 0.1 percent heparin. The mean arterial pressure and heart rate were monitored at 24 hours prior to irradiation.

Food was withheld from the monkeys for 16 hours before irradiation. Water was available during this period ad libitum. Approximately 1 hour before irradiation the animals were transported to the exposure room. In the exposure room the arterial catheter was connected to a Statham* pressure transducer and the transducer's output recorded by a Sanborn† recorder. The venous catheter was attached to a remotely controlled blood collector containing heparinized glass tubes for the blood. At approximately 20 minutes before irradiation a control sample (6 ml) of blood was withdrawn for plasma chemistry studies. Following the withdrawal of the above sample approximately 2.5 μCi of ^{125}I labeled albumin in a volume of 1 ml was injected via the arterial catheter followed by a 1 ml physiological saline suspension of erythrocytes labeled with approximately 4 μCi of ^{51}Cr for blood volume determination.[14] Five minutes before irradiation and at 2, 7, 15, 30, and 60 minutes postirradiation, 6 ml of blood were withdrawn for blood volume and plasma chemistry studies. The animals were removed from the exposure room after the 60-minute postexposure blood collection or after death if it occurred within 60 minutes postexposure. All animals were observed continuously until death; while in the exposure room they were monitored by closed circuit television.

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* Type P23Db pressure transducer, Statham Laboratories Inc., Hato Rey, Puerto Rico

† Eight-channel recorder, Model 7700, Hewlett-Packard Company, Rockville, Maryland

Each monkey was positioned in the exposure room of the AFRRI-TRIGA reactor to receive a calculated dose of 2000, 4000, 15,000, or 50,000 rads of pulsed mixed gamma-neutron radiation. The midline tissue dose (MTD) was obtained by determining the tissue kerma, free-in-air, at the midline exposure volume, and multiplying this value by an experimentally derived factor. For these exposures the operation of the reactor and the characteristics of the radiation field were as previously described.[6,9] The average MTD received and the number of animals in each group are given in Table I. The MTD for each animal within a group was within 5 percent of the average MTD for that group.

Table I. Exposure Schedule

Average midline tissue dose (rads)	Number of animals
Control (sham irradiated)	4
2,100	5
4,200	8
15,600	8
53,200	6

Two milliliters of blood from each collection were transferred to glass tubes for blood volume determinations. The remainder of each sample was centrifuged and the plasma decanted for chemistry determinations. The handling, storage, and methods used for the chemical analyses of the plasma have been previously reported.[12]

III. RESULTS

Arterial Pressure and Heart Rate. The mean arterial pressure (diastolic + 1/3 pulse pressure) and heart rate for each group before irradiation and for 1 hour post-irradiation are plotted in Figures 1 and 2.

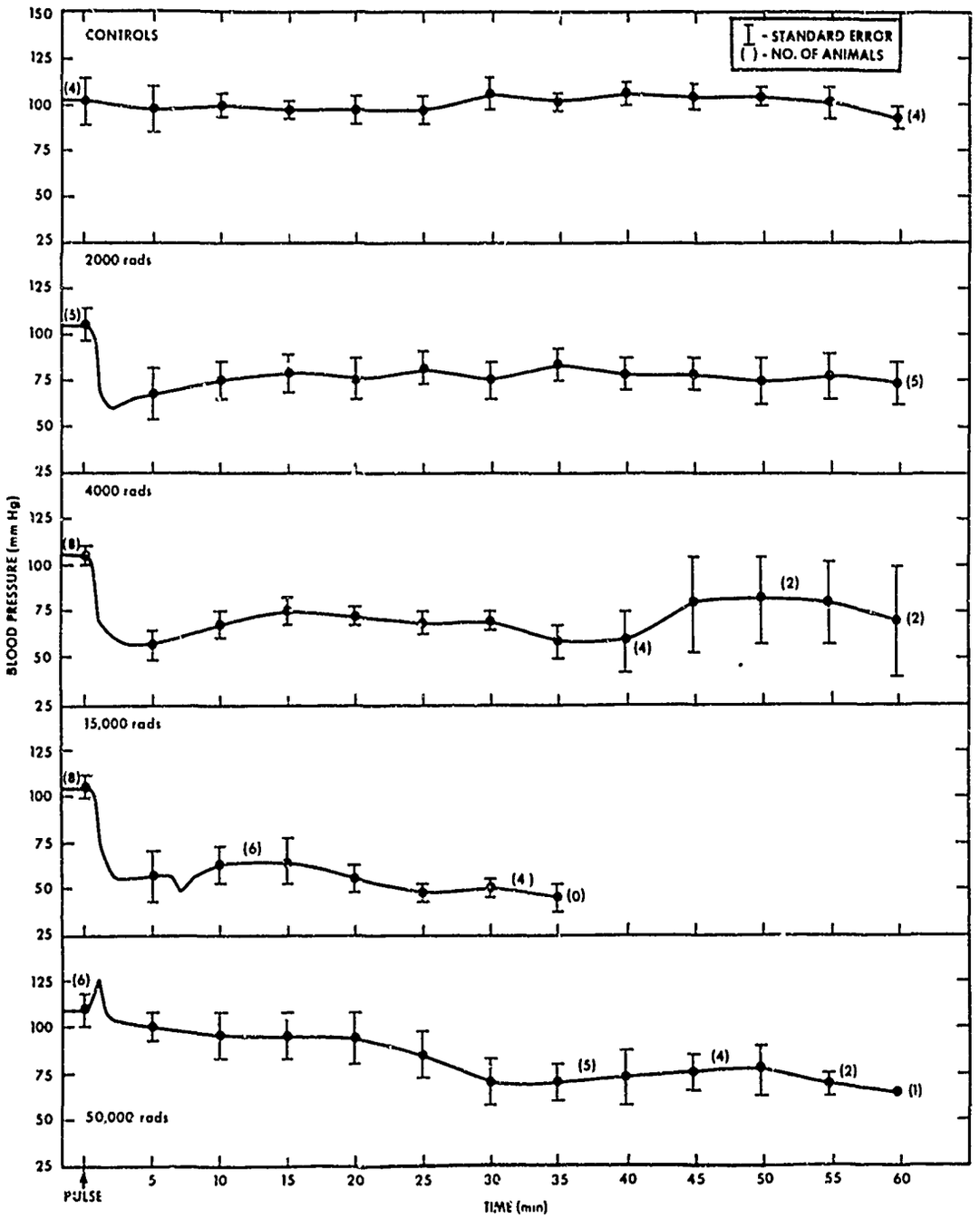

Figure 1. Arterial pressure of monkeys after a supralethal dose of mixed gamma-neutron radiation. The data presented were monitored continuously and were plotted at 1-minute intervals for the first 10 minutes postirradiation and at 5-minute intervals thereafter until death. Some data points and standard errors were omitted in the first 10 minutes postirradiation for clarity.

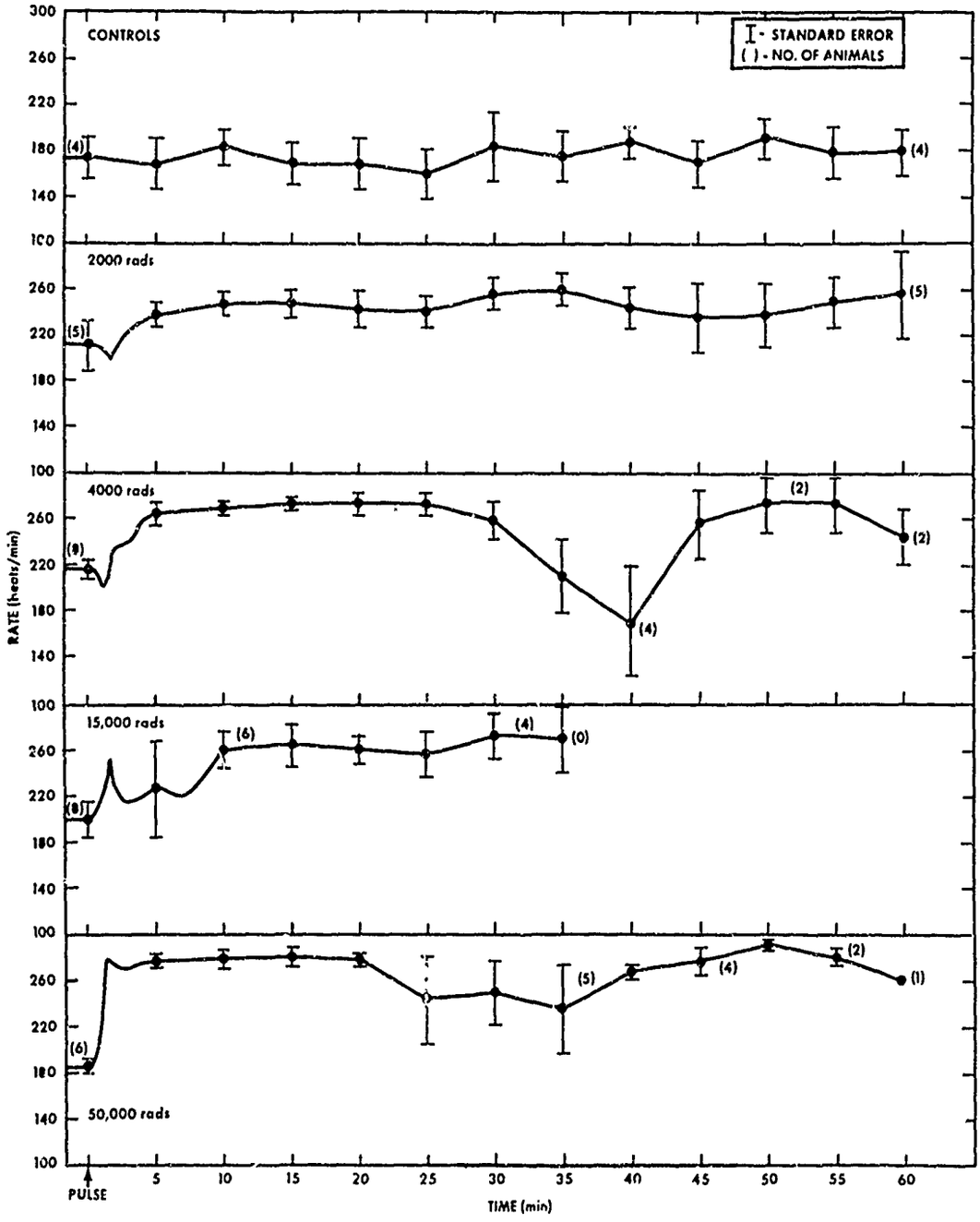

Figure 2. Heart rate of monkeys after a supralethal dose of mixed gamma-neutron radiation. The average heart rate/min was plotted at 1-minute intervals for the first 10 minutes postirradiation and at 5-minute intervals thereafter until death. Some data points and standard errors were omitted in the first 10 minutes postirradiation for clarity.

Within 2 minutes postirradiation a significant decrease in the mean arterial pressure had occurred in the animals receiving a MTD of 2000, 4000, or 15,000 rads. The mean arterial pressure began to return toward normal by 12 minutes postirradiation but did not recover to preirradiation values. Animals that received a 50,000-rad dose experienced a lesser decrease during the first 25 minutes following irradiation which was not significantly lower than preirradiation base lines.

The heart rate increased significantly in the 4000-, and 50,000-rad groups by 3 minutes postirradiation and remained elevated except for an interval from 25 to 45 minutes postirradiation in the 4000-rad group. Animals receiving a 15,000-rad dose displayed considerable variation in heart rate during the first 8 minutes postirradiation after which the heart rates stabilized at significantly elevated values.

From Figures 1 and 2 it should be noted that death of several animals in the 4000-, 15,000-, and 50,000-rad groups occurred from 30 to 40 minutes postirradiation when a marked decrease in heart rate and arterial pressures occurred in some animals. Two animals in the 15,000-rad group died within the first 10 minutes postirradiation. These deaths occurred during the period of extreme fluctuation in heart rate and decreased arterial pressure.

Blood Volume and Plasma Chemistry Values. No significant changes were observed in the red cell volume, plasma volume, or total blood volume. However, the values of the hematocrits tended to remain stable in irradiated animals and to decrease in the sham irradiated controls with successive bleedings postexposure.

Plasma chemistry values were determined at each bleeding for sodium, potassium, chloride, total protein, creatinine, glutamic oxalacetic transaminase, lactic

dehydrogenase, and aldolase. No significant differences in the plasma concentrations of these chemicals were found after irradiation.

IV. DISCUSSION

Several investigators have shown that hypotension occurs in the monkey following doses of 2000 to 6600 rads.[2-4,8] During this period of hypotension a decrement in the performance of a learned task has been observed.[2,5] In the present study the period of hypotension was maximal in the 15,000-rad group. If "gross performance", as observed by Seigneur and Brennan, can be correlated with hypotension, then a hypotensive response could be expected in monkeys receiving doses up to 30,000 rads.[10] This hypotensive response of the monkey to supralethal doses of radiation could be a reflection of vascular engorgement of the abdominal vessels or a general relaxation of the vascular system. However, at higher doses such as 50,000 rads the mechanism by which this early temporary hypotension was initiated appears to be either inhibited or destroyed.

The heart rate generally increased with dose. An increase would be expected as hypotension developed and the heart rate appeared to increase as the blood pressure decreased in the three lower dose groups. However, the largest rate increase occurred in the 50,000-rad dose group without a corresponding decrease in blood pressure. The heart rate can be influenced by pain, apprehension, excitement, and reflex secretion of adrenaline and noradrenaline. The increased heart rate observed following irradiation was probably influenced by more than one of these factors and the contribution of any single factor to the increased rate would be difficult to gauge.

Death of all animals in the study was preceded by respiratory distress culminating in respiratory failure. The onset of respiratory distress was usually preceded by severe hypotension. A number of animals in the 4000-, 15,000-, and 50,000-rad groups died between 30 and 50 minutes postirradiation where a second performance decrement has been reported in the monkey.[5] Two animals died within 10 minutes postirradiation in the 15,000-rad group during the period of severe hypotension. These animals appeared to be unable to maintain a minimal blood pressure necessary for life. The survival times of animals in this study were decreased when compared to other studies where the dose of radiation was similar.[10,13] Factors contributing to the decreased survival times were probably the type of restraint, surgery, and postirradiation blood sampling.

The hematocrits of the irradiated animals tended to remain stable while those of the sham irradiated controls decreased with blood sampling. This indicates that fluid was being lost from the circulatory system and that hemoconcentration did occur after irradiation. With hemoconcentration the plasma components with larger molecular weights would be expected to increase in concentration. Many plasma component concentrations increased, but not significantly, with time postirradiation. They did not increase with the hematocrit as would be expected if the change was due to hemoconcentration alone. It appears that the concentrations of many of the plasma components are significantly affected when sufficient time has elapsed following irradiation for substantial tissue deterioration to occur.[11] In vitro studies have shown that a significant potassuim efflux occurs from tissues and erythrocytes in the first

15 minutes postexposure at high doses of radiation.[1,7] In the present study, an increased plasma concentration of potassium was noted during this period; however, the increase was not significant. It appears that monkeys are capable of maintaining ionic balance after supralethal doses of radiation, probably by excretion of the excess plasma potassium.

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13. ABSTRACT

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